

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 08 January 2001 (08.01.01)	
International application No. PCT/CA00/00482	Applicant's or agent's file reference 1770-224PCT
International filing date (day/month/year) 27 April 2000 (27.04.00)	Priority date (day/month/year) 28 April 1999 (28.04.99)
Applicant PRAKASH, Satya et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
21 November 2000 (21.11.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740 14.35	Authorized officer Nestor Santesso Telephone No.: (41-22) 338 83.38
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PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

SWABEY OGILVY RENAULT
Suite 1600
1981 McGill College Avenue
Montreal, Quebec H3A 2Y3
CANADA

SWABEY OGILVY RENAULT
McGILL COLLEGE

RECEIVED

NOV 14 2000

A.M. 7 8 9 10 11 12 1 2 3 4 5 P.M.

Date of mailing (day/month/year) 02 November 2000 (02.11.00)		
Applicant's or agent's file reference 1770-224PCT 5 C		IMPORTANT NOTICE
International application No. PCT/CA00/00482	International filing date (day/month/year) 27 April 2000 (27.04.00)	Priority date (day/month/year) 28 April 1999 (28.04.99)
Applicant MCGILL UNIVERSITY et al		

- Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AG,AU,DZ,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

- Enclosed with this Notice is a copy of the international application as published by the International Bureau on
02 November 2000 (02.11.00) under No. WO 00/65030

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

by fax and post

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

To:

SWABEY OGILVY RENAULT
Suite 1600
1981 McGill College Avenue
Montreal, Quebec H3A 2Y3
CANADA

FAX NO: (514) 288-8389

Date of mailing
(day/month/year)

29.06.2001

Applicant's or agent's file reference

1770-224PCT FL

IMPORTANT NOTIFICATION

International application No.
PCT/CA00/00482

International filing date (day/month/year)
27/04/2000

Priority date (day/month/year)
28/04/1999

Applicant

MCGILL UNIVERSITY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Büchler, S

Tel. +49 89 2399-8090



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 November 2000 (02.11.2000)

PCT

(10) International Publication Number
WO 00/65030 A3

(51) International Patent Classification⁷: C12N 11/04,
A61K 35/74, 9/50, A61P 3/00

(21) International Application Number: PCT/CA00/00482

(22) International Filing Date: 27 April 2000 (27.04.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/131,468 28 April 1999 (28.04.1999) US

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Montreal, Quebec H3A 2T5 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PRAKASH, Satya
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DuBearn, St-Lambert, Quebec J4S 1K9 (CA).

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1981 McGill College Avenue, Montreal, Quebec H3A 2Y3
(CA).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
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(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

(88) Date of publication of the international search report:
25 January 2001

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: MICROENCAPSULATED GENETICALLY ENGINEERED E. COLI DH 5 CELLS FOR THE REMOVAL OF UN-
DESIRED ELECTROLYTES AND/OR METABOLITES

(57) Abstract: The present invention relates to a composition for the removal of at least one undesired electrolyte and/or metabo-
lite in a patient, which comprises a genetically engineered *E. coli* DH5 cells microencapsulated in artificial cells to be capable of
removing said undesired electrolyte and/or metabolite, wherein said undesired electrolyte is selected from the group consisting of K,
Mg, P, Na, Cl and said undesired metabolite is selected from the group consisting of uric acid, cholesterol, bilirubin, and creatinine,
wherein said removal of undesired electrolyte and/or metabolite lowers the undesired chemical concentration to a therapeutically
acceptable level.

WO 00/65030 A3

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 00/00482

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N11/04 A61K35/74 A61K9/50 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHANG ET AL.: "Therapeutic uses of microencapsulated genetically engineered cells" MOLECULAR MEDICINE TODAY, vol. 4, May 1998 (1998-05), pages 221-227, XP000957917 abstract page 223, right-hand column Box 1.	1-6,8,9
X	WO 97 26903 A (PRAKASH SATYA ;UNIV MCGILL (CA); CHANG THOMAS M S (CA)) 31 July 1997 (1997-07-31) cited in the application page 3, line 1 -page 4, line 28 --- -/--	1-9

☒ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

* Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

2 November 2000

Date of mailing of the international search report

17/11/2000

Name and mailing address of the ISA

European Patent Office P.B. 5818 Patentaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx: 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ceder, O

INTERNATIONAL SEARCH REPORT

Intern 1al Application No

PCT/CA 00/00482

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	<p>PRAKASH ET AL.: "Genetically engineered E. coli cells containing K. aerogenes gene, microencapsulated in artificial cells for urea and ammonia removal" BIOMATERIALS ARTIFICIAL CELLS AND IMMOBILIZATION BIOTECHNOLOGY, vol. 21, no. 5, 1993, pages 629-636, XP000961360 abstract</p> <p style="text-align: center;">---</p>	1-9
A	<p>CA 2 024 196 A (CHANG THOMAS M S ;GAROFALO FLAVIO A (CA)) 14 December 1991 (1991-12-14) abstract; claims</p> <p style="text-align: center;">---</p>	1-5.9
A	<p>EP 0 475 542 A (PREUSSAG NOELL WASSERTECH) 18 March 1992 (1992-03-18) abstract</p> <p style="text-align: center;">---</p>	1
A	<p>US 5 567 451 A (RINN JEAN-CHARLES ET AL) 22 October 1996 (1996-10-22) abstract</p> <p style="text-align: center;">---</p>	1
P,X	<p>PRAKASH ET AL.: "Artificial cell microcapsules containing genetically engineered E. coli DH5 cells for in-vitro lowering of plasma potassium, phosphate, magnesium, sodium, chloride, uric acid, cholesterol, and cratinine: A preliminary report" ARTIFICIAL CELLS BLOOD SUBSTITUTES AND IMMOBILIZATION BIOTECHNOLOGY, vol. 27, September 1999 (1999-09), pages 475-481, XP000961328 the whole document</p> <p style="text-align: center;">-----</p>	1-9

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 5-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 00/00482

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9726903	A	31-07-1997	EP 0876151 A JP 11502875 T	11-11-1998 09-03-1999
CA 2024196	A	14-12-1991	NONE	
EP 0475542	A	18-03-1992	DE 4027219 A	27-02-1992
US 5567451	A	22-10-1996	FR 2673122 A AU 642815 B AU 1423092 A CA 2081314 A DE 69221895 D EP 0637264 A ES 2109349 T WO 9214544 A PT 100157 A, B US 5385741 A	28-08-1992 28-10-1993 15-09-1992 26-08-1992 02-10-1997 08-02-1995 16-01-1998 03-09-1992 31-05-1993 31-01-1995

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference 1770-224PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA00/00482	International filing date (day/month/year) 27/04/2000	Priority date (day/month/year) 28/04/1999
International Patent Classification (IPC) or national classification and IPC C12N5/00		
Applicant MCGILL UNIVERSITY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 21/11/2000	Date of completion of this report 29.06.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Morawetz, R Telephone No. +49 89 2399 8155



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00482

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-22 as originally filed

Claims, No.:

1-16 with telefax of 25/05/2001

Drawings, sheets:

1/13-13/13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA00/00482

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6-9, 10-14.

because:

☒ the said international application, or the said claims Nos. 6-9 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 10-14 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA00/00482

could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 6-9
	No:	Claims 1-5, 15 and 16
Inventive step (IS)	Yes:	Claims
	No:	Claims 6-9
Industrial applicability (IA)	Yes:	Claims 1-5, 15, 16
	No:	Claims

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA00/00482

Re Item I

Basis of the report

1. Amended claims 1-4, 6-9, 14 and 15, filed with the fax dated 25.5.2001 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.
 - 1.1. Claim 1 has been amended to include the feature "metabolically induced". This amendment is considered an unallowable generalisation, because the description as originally filed (page 7, line 10-26) only discloses "metabolic fermentation induction" (emphasis added) but no metabolic induction by any other means also falling within the scope of present claim 1. The same objection applies to claims 2-4, 6-9 and 15.

For the establishment of this report it has been assumed that claims 1 and 15 have been amended to specify that the E. coli cells are metabolically induced by fermentation induction.

- 1.2. Present claim 6 is based on original claim 5 and has been amended to read "in the body" instead of "in plasma". No basis for this amendment has been indicated by the applicant and none could be identified by this authority either. The same objection applies to claims 7-9 and 14.

This report has consequently been established as if this amendment had not been made, since it has been considered to go beyond the disclosure as filed.

2. Claims 5, 10-13, filed with the fax dated 25.5.2001 are considered to fulfill the requirements of Article 34(2)(b) PCT.

Re Item II

Priority

1. The document D7 (PRAKASH ET AL., ARTIFICIAL CELLS BLOOD SUBSTITUTES AND IMMOBILIZATION BIOTECHNOLOGY, vol. 27, September 1999 (1999-09), pages 475-481) indicated in the search report as a P-document

is to be regarded as state of the art according to Article 33(2) PCT for the subject-matter of claims 1-9, 15 and 16, as the date of priority claimed can not be allowed for the relevant parts of the present application.

Please note that the priority document does not disclose the metabolic fermentation induction of the genetically engineered E. coli DH5 cells.

Re Item III

Non-establishment of report with regard to novelty, inventive step or industrial applicability

1. Claims 6-9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
2. It is clear that a fermentation induction procedure is required to change the metabolic enzyme compositions of the genetically engineered E. coli DH5 cells, thereby inducing a metabolic capacity for the removal of undesired electrolytes and/or metabolites. This feature is thus essential to the definition of the invention. Independent claims 10 and 14 do not contain this feature and are consequently so unclear that no meaningful report regarding novelty, inventive step or industrial applicability can be established. The same objection applies to claims 11-13, which are dependent on claim 10.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents, the numbering corresponds to the listing of the documents in the international search report:

D1: CHANG ET AL., MOLECULAR MEDICINE TODAY, vol. 4, May 1998 (1998-05), pages 221-227

D2: WO 97 26903 A

D7: PRAKASH ET AL., ARTIFICIAL CELLS BLOOD SUBSTITUTES AND
IMMOBILIZATION BIOTECHNOLOGY, vol. 27, September 1999

- 2. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-5, 15 and 16 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).**

- 2.1. Present application relates to a composition for the removal of at least one undesired electrolyte and/or metabolite in a patient, which comprises by fermentation induction metabolically induced genetically engineered E. coli DH5 cells microencapsulated in artificial cells to be capable of removing said undesired electrolyte and/or metabolite.

According to the description (page 6, lines 28-32; page 7, line 10 - page 8, line 16; page 9, line 10-13; Examples) genetically engineered E. coli DH5, containing the urease gene from Klebsiella aerogenes were metabolically induced by fermentation induction, microencapsulated in alginate-poly- L-lysine-alginate and than used for the in vitro and in vivo removal studies of plasma K, Mg, P, Na, Cl, cholesterol, bilirubin, uric acid and creatinine.

- 2.2. D7 is the scientific publication corresponding to present application and discloses artificial cell microcapsules containing metabolically induced genetically engineered E. coli DH5 cells for in-vitro lowering of plasma K, Mg, P, Na, Cl, uric acid, cholesterol, creatinine and bilirubine. D7, thus, anticipates the subject-matter of claims 1-5, 15 and 16 (these claims are not entitled to the claimed priority, see item II, above).
- 2.3. The subject-matter of claims 6-9 appears to be novel in view of the available prior art.
- 3. The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claims 6-9 does not involve an inventive step as defined in the regulations (Rule 65 (1)-(2) PCT).**
- 3.1. The disclosure of D7 has been discussed (see paragraph 2.2. above).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA00/00482

D1 and D2, both disclose the use of genetically engineered E. coli DH5, containing the urease gene from Klebsiella aerogenes micro encapsulated in alginate-poly-L-lysine-alginate to remove urea in vitro and in vivo, their potential use for the removal of urea in kidney failure and ammonia in liver failure. This authority is of the opinion, that the subject-matter of claims 6-9 (these claims are not entitled to priority, see item II, above) lacks an inventive step in view of the teaching of D7 combined with D1 or D2.

WHAT IS CLAIMED IS:

1. A composition for the removal of at least one undesired electrolyte and/or metabolite in a patient, which comprises a genetically engineered *E. coli* DH5 cells microencapsulated in artificial cells to be capable of removing said undesired electrolyte and/or metabolite, wherein said undesired electrolyte is selected from the group consisting of K, Mg, P, Na, Cl and said undesired metabolite is selected from the group consisting of uric acid, cholesterol, bilirubin, and creatinine, wherein said removal of undesired electrolyte and/or metabolite lowers the undesired chemical concentration to a therapeutically acceptable level.
2. The composition of claim 1, wherein said *E. coli* DH5 cell is microencapsulated using any microcapsule material which can retain the *E. coli* DH5 cells and allows the undesired electrolyte and/or metabolite for removal to enter the microcapsules.
3. The composition of claim 1, wherein said *E. coli* DH5 cells are entrapped within a carrier using any entrapment material which can retain the cells and allows the undesired electrolyte and/or metabolite for removal to enter in contact with the entrapped cells.
4. The composition of claim 2, wherein said *E. coli* DH5 cells are microencapsulated using any material selected from the group consisting of nylon, silicon rubber, nylon-polyethylenimine, polylactic acid, polyglycolic acid, chitosan-alginate, cellulosesulphate-poly(dimethyldiallyl)-ammonium chloride, hydroxyethyl methacrylate-methyl methacrylate, chitosan-

carboxymethyl-cellulose and alginate-polylysine-alginate.

5. A method of the treatment of a disease with elevated level of undesired electrolytes and/or metabolites in plasma of a patient, which comprises treating said patient with a composition according to claim 1 for the removal of at least one undesired electrolyte and/or metabolite.
6. The method of treatment of claim 5, wherein said disease is a kidney failure-causing disease.
7. The method of treatment of claim 5, wherein said disease is a liver failure-causing disease.
8. The method of treatment of claim 5, wherein said disease is a hyperammonemia with elevated ammonia level.
9. Artificial cells for the *in vitro* removal of at least one undesired electrolyte and/or metabolite in plasma of a patient, which comprises genetically engineered *E. coli* DH5 cells microencapsulated to be capable of removing said undesired electrolyte and/or metabolite, wherein said undesired electrolyte is selected from the group consisting of K, Mg, P, Na, Cl and said undesired metabolite is selected from the group consisting of uric acid, cholesterol, bilirubin, and creatinine, wherein said removal of undesired electrolyte and/or metabolite lowers the undesired chemical concentration to a therapeutically acceptable level.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1770-224PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below	
International application No. PCT/CA 00/ 00482	International filing date (day/month/year) 27/04/2000	(Earliest) Priority Date (day/month/year) 28/04/1999
Applicant MCGILL UNIVERSITY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

MICROENCAPSULATED GENETICALLY ENGINEERED E. COLI DH 5 CELLS FOR THE REMOVAL OF UNDESIRE ELECTROLYTES AND/OR METABOLITES

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38 2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 5-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 00/00482

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N11/04 A61K35/74 A61K9/50 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHANG ET AL.: "Therapeutic uses of microencapsulated genetically engineered cells" MOLECULAR MEDICINE TODAY, vol. 4, May 1998 (1998-05), pages 221-227, XP000957917 abstract page 223, right-hand column Box 1.	1-6,8,9
X	WO 97 26903 A (PRAKASH SATYA ;UNIV MCGILL (CA); CHANG THOMAS M S (CA)) 31 July 1997 (1997-07-31) cited in the application page 3, line 1 -page 4, line 28 -/--	1-9



Further documents are listed in the continuation of box C



Patent family members are listed in annex

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

2 November 2000

Date of mailing of the international search report

17/11/2000

Name and mailing address of the ISA

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Authorized officer

Ceder, O

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/00482

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	PRAKASH ET AL.: "Genetically engineered E. coli cells containing K. aerogenes gene, microencapsulated in artificial cells for urea and ammonia removal" BIOMATERIALS ARTIFICIAL CELLS AND IMMOBILIZATION BIOTECHNOLOGY, vol. 21, no. 5, 1993, pages 629-636, XP000961360 abstract ---	1-9
A	CA 2 024 196 A (CHANG THOMAS M S ;GAROFALO FLAVIO A (CA)) 14 December 1991 (1991-12-14) abstract; claims ---	1-5,9
A	EP 0 475 542 A (PREUSSAG NOELL WASSERTECH) 18 March 1992 (1992-03-18) abstract ---	1
A	US 5 567 451 A (RINN JEAN-CHARLES ET AL) 22 October 1996 (1996-10-22) abstract ---	1
P,X	PRAKASH ET AL.: "Artificial cell microcapsules containing genetically engineered E. coli DH5 cells for in-vitro lowering of plasma potassium, phosphate, magnesium, sodium, chloride, uric acid, cholesterol, and cratinine: A preliminary report" ARTIFICIAL CELLS BLOOD SUBSTITUTES AND IMMOBILIZATION BIOTECHNOLOGY, vol. 27, September 1999 (1999-09), pages 475-481, XP000961328 the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 00/00482

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WO 9726903	A	31-07-1997	EP 0876151 A JP 11502875 T	11-11-1998 09-03-1999
CA 2024196	A	14-12-1991	NONE	
EP 0475542	A	18-03-1992	DE 4027219 A	27-02-1992
US 5567451	A	22-10-1996	FR 2673122 A AU 642815 B AU 1423092 A CA 2081314 A DE 69221895 D EP 0637264 A ES 2109349 T WO 9214544 A PT 100157 A,B US 5385741 A	28-08-1992 28-10-1993 15-09-1992 26-08-1992 02-10-1997 08-02-1995 16-01-1998 03-09-1992 31-05-1993 31-01-1995